Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A method for generating a secondary library of ~~scaffold~~ protein sequences of a target protein comprising:

a) inputting the coordinates of said target protein into a computer;

b) utilizing a forcefield calculation to generate a primary library of primary protein sequences comprising a plurality of primary variant amino acid residues at primary variant positions;

~~a~~c) generating a probability distribution ~~table~~ of amino acid residues in a plurality of variant positions from said force field calculation; and

~~b~~d) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences; wherein at least one of said secondary protein sequences is different from said primary protein sequences.

2. (Currently Amended) A method according to claim 1 ~~further comprising synthesizing a plurality of said secondary sequences.~~ wherein said combining comprises:

a) generating a set of oligonucleotide probes each encoding at least one of said primary variant amino acid residues;

b) using said probes in a polymerase chain reaction (PCR) to generate a plurality of oligonucleotide sequences, each encoding said secondary variant sequences; and

c) producing said secondary variant sequences in host cells transformed with said oligonucleotide sequences.

3. (Currently Amended) A method according to claim 2 wherein said ~~synthesizing~~ PCR is ~~done by~~ multiple PCR and wherein said probes are pooled.

4. (Currently Amended) A method according to claim 3 wherein said ~~pooled oligonucleotides~~ probes are added in equimolar amounts.

5. (Currently Amended) A method according to claim 3 wherein said ~~pooled oligonucleotides~~ probes are ~~added~~ combined in amounts that correspond to the probability of ~~mutation~~ said variant amino acid residues in said probability distribution table.

Claim 6 (cancelled)

7. (New) A method according to claim 1 wherein said target protein is an enzyme.

8. (New) A method according to claim 1 wherein said target protein is a therapeutic protein.

9. (New) A method according to claim 1 wherein the coordinates of a region surrounding a binding site to a receptor is input into a computer.

10. (New) A method according to claim 1 wherein said primary variant positions comprise a region surrounding a binding site.

11. (New) A method according to claim 8 wherein said primary variant positions comprise a region surrounding a binding site to a receptor.

12. (New) A method according to claim 7 wherein said primary variant positions comprise a region surrounding the active site of said enzyme.

13. (New) A method according to claim 7 wherein said primary variant positions comprise a region surrounding the catalytic residues of said enzyme.

14. (New) A method for generating a secondary library of protein sequences of a target protein comprising:

(A) generating a primary library comprising:

(i) inputting the coordinates of a target protein with variable residue positions;

(ii) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue position comprises at least two different amino acid side chains; and

(iii) analyzing the interaction of each of said amino acids with plurality of said amino acids at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences;

(B) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences; and

(C) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants;

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

15. (New) A method for generating a secondary library of protein sequences of a target protein comprising:

(A) generating a primary library comprising:

(i) inputting the coordinates of a target protein with variable residue positions;

(ii) establishing a group of potential rotamers for each of said variable residue positions, wherein the group of potential rotamers for at least one of said variable residue position has a rotamer selected from each of at least two different amino acid side chains; and

(iii) analyzing the interaction of each of said rotamers with plurality of said rotamers at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences;

(B) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences; and

(C) combining a plurality of said amino acid residues from said probability_distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants;

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

16. (New) A method according to claim 14, wherein said force field calculation is Self-Consistent Mean Field (SCMF).

17. (New) A method for generating a secondary library of protein variants of a target protein comprising:

(A) generating a primary library comprising:

(i) inputting the coordinates of a target protein with variable residue positions;

(ii) establishing a group of potential rotamers for each of said variable residue positions, wherein the group of potential rotamers for at least one of said variable residue position has a rotamer selected from each of at least two different amino acid side chains; and

(iii) analyzing the interaction of each of said rotamers with plurality of said rotamers at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences optimized for at least one scoring function;

(B) generating a probability distribution of amino acid residues from said primary library in a plurality of

variant positions from said primary sequences; and

(C) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants;

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

18. (New) A method according to claim 17, wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

19. A method according to claim 14, 15, or 17, wherein said analyzing step utilizes a force field calculation.

20. A method according to claim 14, 15, or 17, wherein said generating step (B) utilizes a force field calculation.

21. A method according to claim 14, 15, or 17, wherein said combining step utilizes a force field calculation.

22. (New) A method for generating a secondary library of protein sequences <u>of a target protein</u> comprising:

a) inputting the coordinates of said target protein into a computer;

b) specifying a list of at least two primary variant positions;

c) utilizing a forcefield calculation to generate a primary library comprising a plurality of primary variant amino acid residues at said primary variant positions;

d) generating a probability distribution of amino acid residues in a plurality of variant positions from a force field calculation; and

e) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences; wherein at least one of said secondary protein sequences is different from said primary protein sequences.

23. (New) A method according to claim 22 wherein said primary library is generated using a monte carlo

search.

24. (New) A method according to claim 22 wherein said primary library is generated using a genetic algorithm.

25. (New) A method according to claim 22 wherein said probability distribution table is derived from frequencies of occurrence in a primary variant library.